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Published in:
Neuropharmacology

DOI:
10.1016/j.neuropharm.2016.07.003

Publication date:
2017

Emerging roles for the novel estrogen-sensing receptor GPER1 in the CNS.

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Keywords: G protein coupled estrogen receptor, hippocampal synaptic function; receptor trafficking; learning and memory; neuroprotection; synaptic plasticity.

Abbreviations

BDNF: Brain derived neurotrophic factor

CNS: Central Nervous System

E2: 17β estradiol

ERα: estrogen receptor alpha

ERβ: estrogen receptor beta

EGFR: epidermal growth factor receptor

ERs: estrogen receptors

ERK: extracellular signal regulated kinase

G1: (±)-1-[(3a*R**,4*S**,9b*S**)-4-(6-Bromo-1,3-benzodioxol-5-yl)-3a,4,5,9b-tetrahydro-3*H*-cyclopenta[*c*]quinolin-8-yl]- ethanone

G15: (3a*S**,4*R**,9b*R**)-4-(6-Bromo-1,3-benzodioxol-5-yl)-3a,4,5,9b-3*H*-cyclopenta[*c*]quinoline

GPER1: G protein-coupled estrogen receptor

LTD: Long term depression

LTP: Long term potentiation

MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine

mTOR: Mammalian target of rapamycin

PI 3-kinase: phosphoinositide 3-kinase

PPR: Paired-pulse facilitation ratio

PPT: propylpyrazole triol

PSD: postsynaptic density

OVX: ovariectomized

SAP97: Synapse-associated protein 97

SC: Schaffer collateral

STAT3: signal transducer and activator of transcription 3

TA: temporoammonic

Abstract.

Estrogens play a key role in regulating reproductive and neuroendocrine function by activating classical nuclear steroid receptors that act as ligand gated transcription factors. However evidence is growing that estrogens also promote rapid non-genomic responses via activation of membrane-associated estrogen receptors. The G protein-coupled estrogen receptor (GPER1; also known as GPR30) has been identified as one of the main estrogen-sensitive receptors responsible for the rapid non-genomic actions of estrogen. In recent years, our understanding of the CNS actions of GPER1s has significantly increased following the development of selective pharmacological tools and via the use of transgenic technologies to knockout GPER1 in mice. Here we review recent advances that have been made to uncover the role of GPER1s in the CNS.

Introduction.

It is well established that the primary female sex hormone estrogen can markedly influence a wide range of physiological processes, including reproductive function. Accumulating evidence also indicates that estrogens have the ability to regulate various neuronal functions, in particular learning and memory (McEwen and Alves, 1999; McEwen et al 2012), with effects of estrogen observed in both male and female brains (Gillies & McArthur, 2010). Numerous studies in rodent and non-human primate models have shown that estrogens enhance cognition and hippocampal learning and memory (Woolley, 2007). Estrogens are also reported to have cognitive enhancing effects in humans, with the effectiveness of estrogens dependent on the women's physiological status (Brinton, 2009).

It is well documented that the central effects of estrogens are mediated by estrogen receptors (ERs) and growing evidence supports a role for both nuclear and membrane-associated ERs in mediating estrogenic effects within the CNS (Vasudevan et al, 2007; Levin 2005). Nuclear ERs are involved in regulating gene transcription by binding to estrogen response elements in the DNA (Hall et al, 2001; Nilsson et al, 2001), whereas the non-genomic effects of estrogens involves activation of membrane-associated receptors that couple to intracellular signalling pathways (Vasudevan et al, 2007; Levin 2005).

Estrogen-sensitive receptors

Classical estrogen receptors (ER) are members of the nuclear hormone receptor superfamily that function as transcription factors to regulate the activity of different genes. Two different

forms of ER, ERα and ERβ have been identified, with considerable sequence homology, but encoded by distinct genes, *ESR1* and *ESR2*, respectively (Gruber et al, 2002). In contrast, non-genomic actions of estrogens involve membrane-associated receptors that activate intracellular signalling pathways following estrogen binding. Membrane-associated ERα and ERβ as well as the novel G-protein coupled estrogen-sensitive receptor, GPER1 are thought to mediate the rapid non-genomic actions of estrogens (Srivastava et al, 2013).

GPER1 expression in the brain

Several studies have examined the localisation of GPER1 in rodent brain and have reported high levels of GPER1 expression in both cortical and hippocampal regions (Brailoiu et al, 2007; Hazell et al, 2009; Almey et al, 2014; Almey et al, 2015). Expression of GPER1 has also been detected in the basal forebrain, thalamus and dorsal striatum (Brailoiu et al, 2007; Hazell et al, 2009). In addition, the subcellular distribution of GPER1 has been probed in the dorsal striatum and hippocampal CA1 region. In the dorsal striatum of adult female rats, GPER1 immunolabelling is associated with both glia and neurons (Almey et al, 2012). Ultra-structural analyses have revealed that GPER1 expression is not only restricted to extranuclear sites within the dorsal striatum, but also that GPER1 is highly localised to dendritic spines (Almey et al, 2012). Similarly in hippocampal CA1 neurons, GPER1 immunoreactivity is associated with dendritic spines and is specifically localised to the postsynaptic density (PSD; Akama et al, 2013; Waters et al, 2015). Dual-labelling studies in cortical neurons also suggest synaptic expression of GPER1 as GPER1-positive immunolabelling colocalises with the presynaptic protein, bassoon (Srivastava and Evans, 2013).

In line with other G protein-coupled receptors that are classical seven transmembrane spanning receptors, several studies have reported expression of GPER1 at the plasma membrane in hippocampal neurons (Filardo et al, 2007; Akama et al, 2013; Funakoshi et al, 2006). However, there is also strong evidence supporting GPER1 expression on intracellular structures such as the endoplasmic reticulum (Revankar et al, 2005; Prossnitz et al, 2009). Studies in cancer cell lines have suggested that both plasma-membrane or intracellular GPER1s can mediate the rapid non-genomic effects of estrogens as the endogenous ligand, E2 is membrane permeable and can readily access GPER1 at either locus (Revankar et al, 2005; Srivastava and Evans, 2013). Thus it is likely that neuronal GPER1s that are expressed at the plasma membrane or on intracellular organelles can also be rapidly activated by E2.

GPER1 signalling.

As a member of G-protein coupled receptor superfamily, GPER1 couples to G proteins with subsequent modulation of second messenger signalling cascades. The signalling pathways that are activated by GPER1 in cancer cells are well documented. GPER1 activation involves $G\alpha_s$ stimulation leading to activation of adenylate cyclase and a subsequent increase in cAMP levels. However, GPER1 can also couple to a pertussis toxin sensitive $G\alpha_{i/o}$ protein resulting in activation of phosphoinositide 3-kinase (PI 3-kinase) or activation of Src protein kinase (Src) and recruitment of the adaptor protein SHC (Src-Homology-Containing) leading to transactivation of the epidermal growth factor receptor (EGFR; Prossnitz et al, 2011; Filardo et al, 2012; Figure 1). Once activated, EGFR results in stimulation of the ERK (extracellular signal regulated kinase) signalling cascade (Prossnitz et al, 2011; Filardo et al, 2012). GPER1 is also reported to elevate intracellular Ca^{2+} levels and a number of different signalling mechanisms have been proposed, including phospholipase C (Revankar et al, 2005), inositol receptor and ryanodine receptor (Ariazi et al, 2010). $G\alpha_{i/o}$ is also implicated in GPER1-driven Ca^{2+} signalling as pertussis toxin inhibits the ability of GPER1 to raise intracellular Ca^{2+} levels in COS7 cells (Revankar et al, 2005).

In neurons GPER1 is reported to couple to PI 3-kinase and/or ERK signalling cascades to regulate cell viability (Gingerich et al, 2010; Abdelhamid et al, 2011; Liu et al, 2012). Recent studies indicate that GPER1 activation leads to mTOR phosphorylation downstream of PI 3-kinase, and this process is required for GPER1-mediated stimulation of BDNF release in hippocampal neurons (Briz and Baudry, 2014). However, there is some controversy as to whether GPER1-driven activation of PI 3-kinase/Akt signalling involves Gαi/o or not. Several lines of evidence support the involvement of $G\alpha_{i/o}$ (Filardo et al, 2000; Ding et al, 2009), however a pertussis-toxin insensitive pathway is also reported to mediate the activation of PI 3-kinase/Akt signalling downstream of GPER1 (Revankar et al, 2005). In hypothalamic arcuate nucleus neurons, application of the GPER1 agonist, G1 stimulates phosphorylation of STAT3 and this process is hypothesised to contribute to the anorectic effects of estrogens (Kwon et al, 2014).

The pharmacology of GPER1

Selective pharmacological tools for GPER1 have been developed that have enabled greater understanding of the role of GPER1 in mediated estrogenic responses. In this respect, the

GPER1 agonist, G1 and antagonist, G15 have been utilised extensively (Langer et al, 2010). Although, G1 and G15 do not bind to ERα or ERβ (Bologa et al, 2006; Dennis et al, 2009), recent studies have suggested that ERα36, a splice variant of ERα is also a target for G1in some cell types (Kang et al, 2010). However, the ability of G1 to promote neuritogenesis was blocked by G15 or following knockdown of GPER1, suggesting the involvement of GPER1 but not ERα36, even though ERα36 is expressed in hippocampal neurons (Puiz-Palmero et al, 2013).

The anti-estrogen agent, ICI 182,780 (fulvestrant) which is an antagonist at ERα and ERβ, and the selective estrogen receptor modulator, tamoxifen are both reported to have agonist activity at GPER1 (Thomas et al, 2005). In MCF-7 breast cancer cells, ICI 182,780 enhances cell-matrigel adhesion via activation of GPER1 (Chen et al, 2014). Moreover, in endometrial cancer cells that lack ERα, tamoxifen promotes cell migration via activation of GPER1 (Tsai et al, 2013). ICI 182,780 is also reported to have GPER1 agonist activity in neurons as application of ICI 182,780 to hippocampal neurons increased neurogenin 3 expression and neuritogenesis, which mirrored the effects of G1 and E2 (Ruiz-Palmero et al, 2013; Ruiz-Palmero et al, 2011). Moreover the effects of ICI 182,780 were blocked by G15 and following knockdown of GPER1 (Ruiz-Palmero et al, 2013). Recent studies indicate that the "selective" ERα agonist, propylpyrazole triol (PPT), also has agonist actions at GPER1 (Petrie et al, 2013), which further complicates interpretation of data using this compound.

Four transgenic mouse models with knockdown of GPER1 have been developed in recent years and used to examine GPER1 physiology and function (Wang et al, 2008; Mårtensson et al, 2009; Otto et al, 2009; Isensee et al, 2009). For instance, GPER1 is implicated in estrogen-induced thymic atrophy as G1 induces thymic atrophy and apoptosis of thymocytes; effects that are attenuated in GPER1-deficient mice (Wang et al, 2008). In addition, GPER1 is linked to key metabolic functions as GPER1-deficient mice display impairments in glucose tolerance as well as loss of estrogen-stimulated release of insulin (Mårtensson et al, 2009). Studies in GPER1 knock out mice have also identified roles for GPER1 in the CNS (Prossnitz and Hathaway, 2015). Thus, GPER1 deficiency is associated with significant weight gain in female rats, suggesting that GPER1 is involved in the hypothalamic control of energy homeostasis (Davis et al, 2014). This possibility is supported by the finding that GPER1-deficient mice are less sensitive to estrogenic effects on food intake than wild type littermates (Davis et al, 2014). GPER1 is also implicated in the anxiogenic effects of E2 as

GPER deficiency is associated with alterations in anxiety levels and the stress response (Kastenberger and Schwarzer, 2014). In agreement with this, systemic injection of the GPER1 agonist G1 into mice results in the induction of anxiety-like behaviours (Kastenberger et al, 2012). Thus emerging evidence indicates a prominent role for GPER1 in regulating various neurological functions and as a consequence targeting the GPER1 system may be of novel therapeutic benefit in particular CNS-driven diseases.

Most evidence points to E2 as the endogenous ligand for GPER1 (Thomas et al, 2006; Thomas et al, 2010) although some studies have contested this (see Maggiolini & Picard, 2010 for a review). More recent controversial findings have suggested that the steroid aldosterone is also an agonist at GPER1 in vascular smooth muscle cells overexpressing GPER1 (Gros et al, 2011). However questions have been raised about whether these findings truly reflect the properties of native GPER1s (Filardo and Thomas, 2012). Emerging evidence suggests that GPER1 displays non-classical pharmacology (biased agonism), such that different agonists for GPER1 induce distinct receptor configurations thus enable coupling to divergent second messenger systems (Srivastava et al, 2005; Evans et al, 1995). Moreover the cellular localisation of GPER1 and the density of G proteins in specific cell types are thought to markedly influence GPER1 pharmacology (Srivastava and Evans, 2013). Recent studies suggest that GPER1 may associate with other GPCRs, such as the corticotropin releasing hormone receptor (Akama et al, 2013), or form receptor complexes with scaffolding proteins like SAP97 and PSD-95 (Waters et al, 2015; Akama et al, 2013), which is also likely to impact on GPER1 pharmacology.

Estrogens and the regulation of hypothalamic function

It is well established that E2 secreted from the ovaries signals to the brain and activates the circuits controlling ovulation. Within the hypothalamic pituitary-ovarian axis, E2 regulates the release of gonadotropin-releasing hormone (GnRH) and lutenizing hormone (LH) as well as stimulating sexual behaviour (Micevych and Kelly, 2012). In the arcuate nucleus, E2 rapidly regulates the excitability of GnRH neurons (Kelly et al, 1984) via activation of inward rectifying K^+ channels and K_{ATP} channels (Kelly et al, 1984; Lagrange et al, 1995; Zhang et al, 2010). E2-driven modulation of voltage-gated Ca^{2+} channel activity is also implicated in the regulation of hormone release and neuronal excitability in GnRH neurons (Zhang et al, 2009). Recent studies indicate that GPER1 may contribute to E2-mediated regulation of Ca^{2+} signalling as the GPER1 agonist G1 mirrored the facilitation of Ca^{2+}

currents induced by E2 in GnRH neurons (Sun et al, 2010). In support of a role for GPER1, the ability of E2 to modulate Ca^{2+} oscillations in primate GnRH neurons is mimicked by G1 and attenuated following knockdown of GPER1 (Noel et al, 2009). Moreover, recent studies have identified that GPER1 may mediate, in part, the rapid negative feedback of GnRH-induced secretion of LH by E2 in bovine gonadotrophs (Rudolf and Kadokawa, 2013).

In addition to controlling reproductive function, E2 plays an important role in the hypothalamic regulation of energy homeostasis. Indeed, E2 has clear anoretic effects as an ERα loss of function mutation results in an obese phenotype in man (Smith et al, 1994), whereas selective knockdown of ERα in mouse brain results in hyperphagia and a clear metabolic phenotype (Geary et al, 2001; Park et al, 2011). Recent compelling evidence indicates that rapid signalling via membrane ERs plays a role in energy homeostatic mechanisms (Qiu et al, 2006). It is likely that GPER1 is the membrane ER involved as knockdown of GPER1 not only results in a significant weight gain in female rats but also reduced sensitivity to the anorectic effects of E2 (Davies et al, 2014).

Estrogens and dendritic spine re-modelling

Early studies have demonstrated fluctuations in the density of dendritic spines during the oestrous cycle as well as loss of dendritic spines following ovariectomy (Gould et al, 1990; Woolley et al, 1990), suggesting that estrogenic hormones may influence spine remodelling. Attenuated levels of E2, due to inhibition of aromatase activity, are also linked to hippocampal dendritic spine loss (Kretz et al, 2004); an effect that is rescued by treatment with E2 (Zhou et al, 2007). Several studies indicate that the effects of E2 on dendritic morphology is at least in part due to non-genomic mechanisms. Indeed, rapid increases in the density of dendritic filopodia are evident after 20-30 min exposure of cortical or hippocampal neurons to E2 (Sanchez et al, 2009; Murakami et al, 2006). Real time imaging studies have also revealed rapid alterations in dendritic spine morphology and density after short term treatment with E2 (Srivastava et al, 2008; Mukai et al, 2007).

The classical ERs, ERα and ERβ are localised to dendritic spines (Milner et al; 2001; Milner et al, 2005; Romeo et al, 2005; Mitterling et al, 2010) and both receptor subtypes are thought to mediate the rapid effects of E2 on dendritic morphology (Sellers et al, 2015; Zhou et al, 2014; Murakami et al, 2006; Mukai et al, 2007). However recent evidence suggests that GPER1 may also play a role (Akama et al, 2013; Waters et al, 2015). Indeed, in hippocampal neurons GPER1 positive-immunoreactivity is associated with dendritic spines and is localised

to the postsynaptic density (PSD; Waters et al, 2015). Moreover, in biochemical assays the C-terminal domain of GPER1 binds to PDZ domains of the spine scaffolding protein PSD-95 (Akama et al, 2013). In addition, GPER1 has been shown to co-immunoprecipitate with SAP97 (Waters et al, 2015), a postsynaptic scaffolding protein that is linked to recycling of receptors within dendritic spines (Magalhaes et al, 2012). Thus there is growing evidence that GPER1 is well positioned to mediate the rapid non-genomic effects of E2 on dendritic spine morphology and function. Although most evidence points to a postsynaptic locus for GPER1, recent ultrastructural analyses has also found GPER1 expression at presynaptic terminals and in glia cells (Waters et al, 2015). Identification of GPER1-positive immunolabelling within presynaptic terminals suggests a possible role for GPER1 in regulating neurotransmitter release mechanisms. The high density of GPER1 associated with glia cells may be a linked to a neuroprotective role as glial cells are implicated in the neuroprotective actions of E2 (Sortino et al, 2004). However, further studies are required to verify how the distribution of GPER1s influences its impact on neuronal function.

Regulation of hippocampal synaptic plasticity

Two of the main forms of activity-dependent synaptic plasticity, namely long-term potentiation (LTP) and long-term depression (LTD) occur in the hippocampus and are thought to be cellular correlates of spatial learning and memory (Bliss and Collingridge, 1993). A number of hormones and growth factors, including estrogens, are reported to influence hippocampal synaptic plasticity. Indeed, application of E2 to acute hippocampal slices not only facilitates NMDA receptor function (Smith and McMahon, 2006; Foy et al, 1999) but also enhances the magnitude of LTP (Foy et al, 1999; Kramar et al, 2009). Activation of ERβ, but not ERα, is reported to mediate the facilitation of LTP by E2 (Kramar et al, 2009). Conversely, E2 promotes the facilitation of LTD at hippocampal synapses and this occurs via an ERα-dependent mechanism (Mukai et al, 2007).

Several studies have documented that GPER1 can also alter the efficacy of excitatory synaptic transmission at the Schaffer-collateral input to hippocampal CA1 (SC-CA1) synapses. Indeed, the GPER1 agonist G1 is reported to mirror the actions of E2 as a persistent increase in excitatory synaptic transmission at CA1 synapses was evident in hippocampal slices treated with G1 (Smejkalova and Woolley, 2010). The ability of E2 or G1 to increase synaptic transmission was paralleled by a decrease in the paired pulse ratio (PPR), suggesting involvement of a presynaptic mechanism. Moreover, application of the putative GPER1

agonist, ICI 182,780 also resulted in an increase in hippocampal synaptic transmission that was associated with a decrease in PPR (Smejkalova and Woolley, 2010). Thus it is likely that activation of GPER1 contributes, at least in part, to the E2-induced potentiation of excitatory synaptic transmission at hippocampal SC-CA1 synapses. Recent studies also suggest that E2 has the ability to modulate excitatory synaptic strength at the temporoammonic input to CA1 (TA-CA1) neurons (Smith et al, 2016), however the contribution of GPER1 to this effect of E2 is not known.

More recent studies have suggested a role for GPER1 in a novel form of LTD induced at hippocampal CA3 synapses. Indeed, GPER1 acts in concert with metabotropic glutamate receptors (mGluRs) to depress excitatory synaptic transmission via a mechanism involving release of BDNF and internalisation and degradation of the AMPA receptor subunit, GluA1 (Briz et al, 2015).

Regulation of glutamate receptor trafficking

Glutamate receptor trafficking plays a key role in hippocampal activity-dependent synaptic plasticity (Collingridge et al, 2004). During hippocampal LTP, activation of NMDA receptors accelerates trafficking of AMPA receptors to synapses (Man et al, 2003). Moreover, dynamic alterations in the actin cytoskeleton is implicated in hippocampal synaptic plasticity (Fukazawa et al, 2003), and the regulation of AMPA receptor trafficking processes (Zhou et al, 2001). Thus, as E2 modulation of LTP and dendritic spine morphology is linked to alterations in actin dynamics, it is likely that E2 also promotes alterations in glutamate receptor trafficking. Indeed, studies by Srivastava et al (2006) were the first to demonstrate that treatment of cortical neurons with E2 resulted in transient removal of GluA1 from synapses; an effect that was accompanied by the synaptic insertion of the NMDA receptor subunit GluN1 suggesting formation of silent synapses. Conversely, increases in GluA1 surface expression have been observed in hippocampal neurons exposed to E2 (Zadran et al, 2009; Potier et al, 2015); an effect that has been attributed to the activation of ERβ as selective ERβ agonists mirror the E2-induced rise in surface GluA1 expression (Liu et al, 2008; Kramar et al, 2009). The subunit composition of hippocampal synaptic AMPA receptors also changes during the estrous cycle, indicating that fluctuations in endogenous estrogen levels also influence AMPA receptor trafficking *in vivo* (Tada et al, 2015). Moreover, real time imaging studies have revealed rapid modulation of hippocampal NMDA receptor trafficking as acute exposure to E2 attenuates GluN2B surface expression, with no effect on surface GluN2A in hippocampal neurons (Potier et al, 2015). Although most studies

have focussed on the role glutamate receptor trafficking in synaptic plasticity mechanisms during early postnatal development, activity-dependent alterations in the mobility of glutamate receptors also occurs in adult and aged hippocampus (Moga et al, 2006). Furthermore, estrogen is reported to regulate NMDA receptor expression in an age-dependent manner as the density of GluN1 subunits at CA1 synapses is increased by estrogen in the hippocampus of aged, but not young rats (Adams et al, 2004).

Although there have been limited studies examining the effects of GPER1 on glutamate receptor trafficking, recent evidence indicates that exposure to the GPER1 agonist, G1 reduces GluA1 surface expression in the hippocampal CA3-dentate gyrus region (Briz et al, 2015). In contrast to the effects of E2, the effects of G1 were observed after 60 min exposure to the GPER1 agonist and involved activation of mTOR-dependent protein translation (Briz et al, 2015). Further studies are required to fully delineate the cellular mechanisms underlying GPER1 regulation of glutamate receptor trafficking events.

Estrogen and memory and cognition

The ability of estrogens to regulate memory function and cognition has been extensively studied with analyses ranging from basic investigations in rodent models to translational and clinical studies in humans. Multiple studies in rodents have identified that estrogens markedly influence cognitive processes including learning and memory. Indeed, deficits in working and spatial memory tasks are evident in ovariectomized (OVX) female rats (Daniel et al, 1997; Gibbs and Johnson, 2008); actions that are reversed with acute treatment with various estrogens (Daniel et al, 1997; Gibbs and Johnson, 2008). In addition, rapid effects of estrogens on memory processes has been widely reported in various mouse models (Choleris et al, 2012; Frick, 2009). Moreover, studies using selective pharmacological tools and transgenic mice indicate a role for both ERα and ERβ in mediating the rapid effects of estrogens on cognitive function (Walf et al, 2006; Walf et al, 2008; Liu et al, 2008).

However evidence is growing that GPER1 activation also influences cognition. Studies by Hammond et al (2009) were the first to show that GPER1 activation has a beneficial effect on cognitive function. Indeed, chronic treatment of OVX rats with the GPER1 agonist, G1 restores the rate of acquisition in a spatial learning task compared to control rats (Hammond et al, 2009). Subsequent studies from this group provide further support for the cognitive enhancing effects of GPER1 as inhibition of GPER1 with G15 impaired spatial learning in

OVX and gonadally intact rats treated with E2 (Hammond et al, 2012). Rapid improvements in various hippocampal dependent learning paradigms (social recognition learning, object recognition and object placement) are observed 40 min after administration of G1 (Gabor et al, 2015). Short term application of a GPER1 agonist also enhances spatial recognition memory in rats; an effect that parallels the actions of E2 (Hawley et al, 2014). Furthermore activation of GPER1, but not ERα or ERβ, mirrors the rapid enhancement of social learning induced by E2 (Ervin et al, 2015). But, emerging evidence indicates that GPER1 enhances hippocampal memory via distinct signalling pathways to E2 (Frick, 2015), suggesting that the effects of GPER1 on memory may be independent of E2. Further studies are required to determine the precise cellular processes underlying GPER1 regulation of hippocampal memory and cognition.

Recent studies suggest that GPER1 activation may also contribute to the ability of E2 to enhance cognitive performance by regulation of the cholinergic afferents that innervate the hippocampus and cortex (Hammond and Gibbs, 2011; Gibbs et al, 2014). Indeed, high levels of GPER1 are not only expressed on basal forebrain cholinergic neurons (Hammond and Gibbs, 2011), but GPER1 activation enhances K^+-stimulated release of ACh from cholinergic neurons as well as the release of ACh associated with feeding (Gibbs et al, 2014). Thus these findings suggest that GPER1 has the ability to regulate hippocampal memory and cognitive function via either direct actions on hippocampal synaptic function, or by indirectly influencing the activity of cholinergic inputs to the hippocampus.

Estrogen and neuroprotection

Estrogens have powerful neuroprotective properties in rodents and humans. Some of the earliest studies suggested a neuroprotective role for E2 as gonadally-intact female rats sustained less neuronal cell death than age-matched males following cerebral ischemia-reperfusion injury (Simpkins et al, 1997). Numerous *in vivo* studies support these initial findings and demonstrate neuroprotective effects of estrogens in various rodent models of acute cerebral ischemia (Dubal et al, 1998; Sudo et al, 1997; Fukuda et al, 2000). Potent neuroprotective effects of E2 are also widely reported in a range of cellular models of neurotoxicity induced by oxidative stress, excitotoxicity and β-amyloid (Simpkins et al, 2012; Marin et al, 2012). Moreover, clinical evidence indicates that post-menopausal women have a greater risk of stroke and neurodegenerative disease following loss of endogenous estrogens (Brinton 2009). Although most evidence suggests a role for either ERα or ERβ in mediating

the neuroprotective actions of estrogens, several recent studies also indicate neuroprotective actions of GPER1. Thus, acute application of the GPER1 agonist G1 reduced ischemia-damage to hippocampal neurons in aged female rats (Lebesgue et al, 2010). In addition, GPER1 activation mirrors the effects of E2 by increasing the survival of cortical and hippocampal neurons exposed to neurotoxic insults (Gingerich et al, 2010; Liu et al, 2011; Liu et al, 2012). The cellular mechanisms underlying the neuroprotective actions of GPER1 involve activation of ERK1/2 signalling (Liu et al, 2012; Liu et al, 2011) and are associated with selective downregulation of GluN2B-containing NMDA receptors (Liu et al, 2012).

Recent evidence indicates that GPER1 activation has beneficial actions in neurodegenerative disease. Thus treatment with the GPER1 agonist G1 protects nigrostriatal dopaminergic neurons against MPTP-induced toxicity in a mouse model of Parkinson's disease (Bourque et al, 2015). Moreover, MPTP toxicity is elevated in MPTP mice treated with the GPER1 antagonist, G15 (Bourque et al, 2013; Al-Sweidi et al, 2011). As activation of GPER1 stimulates pro-survival signalling cascades in various models of toxicity, it is likely that GPER1 activation will also exhibit protective actions in other neurodegenerative disease models.

Conclusions.

Substantial evidence indicates that estrogens markedly influence numerous CNS functions, including learning and memory, and neuronal survival (Fig 2). Rapid responses induced by membrane-associated ERs are thought to mediate many of the central effects of estrogens. The classical ERs, ERα and ERβ contribute to some rapid CNS estrogenic responses. However, emerging evidence suggests that the recently identified GPER1 is one of the main estrogen-sensitive receptors responsible for the rapid non-genomic actions of estrogen. Recent localisation studies indicate that GPER1 is enriched in the brain and it is in a prime position to regulate synaptic function as it is also highly expressed at synapses. Indeed, activation of GPER1 regulates diverse aspects of hippocampal synaptic function, with potent rapid effects reported on dendritic morphology and activity-dependent synaptic plasticity. Emerging data indicates that GPER1 activation can also influence higher brain functions such as cognition, however the precise cellular mechanisms involved in GPER1 regulation of memory and cognition remained to be established. A role for GPER1 in mediating the neuroprotective actions of estrogens is also becoming apparent, as several studies indicate that GPER1 has the ability to protect neurons from a variety of toxic insults. Moreover,

GPER activation promotes neuronal survival in models of Parkinson's disease, suggesting a potential beneficial role for GPER1 in various neurodegenerative disorders.

Acknowledgements

J.H. acknowledges support from The Anonymous Trust and Cunningham Trust.

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Figure 1.

Schematic overview of the key GPER1 signalling pathways.

The primary signalling cascades activated by GPER1 involve stimulation of Gαs and Gαi/o resulting in the activation and inhibition of adenylate cyclase activity, respectively. GPER1-driven stimulation of Gαi/o is also reported to result in the activation of PI 3-kinase/Akt-dependent signalling, as well as the transactivation of the EGFR via activation of Src protein kinase (src), recruitment of Src-homology-containing adapter protein (SHC), activation of matrix metalloproteinase (MMP) and subsequent liberation of heparin-bound epidermal growth factor (HB-EGF). Furthermore, activation of GPER1 increases the intracellular levels of Ca^{2+}; an effect that is also thought to involve $G\alpha_{i/o}$ stimulation.

Figure 2.

Schematic representation of the key neuronal functions that are regulated by GPER1.

E2 activation of membrane-associated GPER in hippocampal neurons results in the initiation of rapid signalling events and subsequent modulation of key hippocampal and hypothalamic functions. In rodent hippocampus GPER1 activation leads to rapid modulation of dendritic morphology and excitatory synaptic transmission. The ability of GPER to regulate hippocampal synaptic function is likely to contribute to GPER-mediated enhancement of hippocampal memory and cognition. Recent studies have highlighted neuroprotective actions of GPER as neuronal viability is increased following treatment with GPER agonists. Moreover, activation of GPER may be beneficial in neurodegenerative disorders as GPER activation is reported to enhance neuronal survival in cellular models of Parkinson's disease. GPER1 activation is also thought to play a key role in mediating the effects of E2 on key hypothalamic functions, including energy homeostasis and reproductive function.